AUSTRALIAN PRODUCT INFORMATION

ZIAGEN (abacavir)
tablets and oral solution

ZIAGEN (abacavir) is associated with hypersensitivity reactions, which can be life-threatening and in rare cases fatal. ZIAGEN, or any other medicinal product containing abacavir (TRIUMEQ, TRIZIVIR, KIVEXA), MUST NEVER be restarted following a hypersensitivity reaction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

1 NAME OF THE MEDICINE

Abacavir (as sulfate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Abacavir sulfate is a white to off-white crystalline powder with a solubility of approximately 77 mg/mL in water at 25°C.

ZIAGEN is supplied in tablets containing 300 mg of abacavir (as sulfate).

ZIAGEN is supplied in oral solution containing 20 mg/mL of abacavir (as sulfate). ZIAGEN oral solution also contains sorbitol solution (70%), saccharin sodium, methyl hydroxybenzoate and propyl hydroxybenzoate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablets
The unscored film-coated tablets are yellow, biconvex, capsule shaped and engraved with “GX 623” on one side.

The scored film-coated tablets are yellow, biconvex, capsule shaped and engraved with “GX 623” on both sides.

Oral solution
The oral solution is a clear to slightly opalescent yellowish aqueous solution which may turn into a brown colour over time with strawberry/banana flavouring.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZIAGEN (abacavir) is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children (see Section 5.1

PHARMACODYNAMIC PROPERTIES - Clinical trials). This indication is based on surrogate endpoints in studies up to 48 weeks in duration.

4.2 DOSE AND METHOD OF ADMINISTRATION

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing.

For patients who are unable to swallow tablets, the tablet(s) may be crushed and 100% of the crushed tablet could be added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. Alternatively, abacavir is available as an oral solution. More accurate dosing can be achieved with the oral solution of abacavir.

Tablets:

Weight (kg)	Once-Daily Dosing Regimen	Twice-Daily Dosing		Total Daily Dose
		AM Dose	PM Dose	
14 to <20	1 tablet (300 mg)	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
≥20 to <25	1 ½ tablets (450 mg)	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥25	2 tablets (600 mg)	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Children ≥ three months and weighing less than 25 kg
A dosing regimen according to weight bands is recommended for ZIAGEN scored tablets and oral solution. This dosing regimen for paediatric patients weighing 14 - 25 kg is based primarily on pharmacokinetic modelling. Clinicians should be aware that variability in drug exposures is possible and patients should be monitored accordingly.

Children weighing < 14 kg
ZIAGEN scored tablets should not be used for children weighing less than 14 kg, since doses cannot be appropriately adjusted for the weight of the child. For these patients and for patients, who are unable to swallow tablets, oral solutions should be used.

Oral solution:

Weight (kg)	Once-Daily Dosing Regimen	Twice-Daily Dosing		Total Daily Dose
		AM Dose	PM Dose	
≥3mths to <25 kg	16mg/kg	8mg/kg	8mg/kg	Max 600 mg
≥25	30 mL (600mg)	15 mL (300 mg)	15 mL (300 mg)	600 mg

Children less than three months
There are no data available on the use of ZIAGEN in this age group.

Food reduces the C_{max} and extends the T_{max} of abacavir but the amount of drug absorbed is not reduced. The clinical significance of this is not known (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Data regarding the efficacy of once-daily dosing in paediatric population is limited to patients who transitioned from twice-daily to once-daily dosing after 36 weeks of treatment (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Renal impairment
The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Hepatic impairment
Abacavir is metabolised primarily by the liver. The recommended dose of abacavir in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg (10 mL) twice a day. To enable dose reduction abacavir oral solution should be used for the treatment of these patients. Pharmacokinetic and safety data on the use of abacavir in patients with moderate and severe hepatic impairment are not available (see Section 5.2 PHARMACOKINETIC PROPERTIES). Therefore, the use of abacavir is not recommended in patients with moderate or severe hepatic impairment, unless the benefit of use outweighs the risk.

4.3 CONTRAINDICATIONS

ZIAGEN is contra-indicated in patients with known hypersensitivity to abacavir or to any ingredient of the preparation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity – special warning

Hypersensitivity to abacavir (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))
Hypersensitivity to abacavir is a multi-organ clinical syndrome which can occur at any time during treatment, but most often occurs within the first 6 weeks of therapy. Signs or symptom usually present in 2 or more of the following groups although hypersensitivity following the presentation of a single sign or symptom has been reported infrequently.

- fever
- rash
- gastrointestinal, including nausea, vomiting, diarrhoea, or abdominal pain
- constitutional, including generalized malaise, fatigue, or achiness
- respiratory, including dyspnoea, cough, or pharyngitis.

Hypersensitivity reactions may present similarly to pneumonia, bronchitis or pharyngitis, influenza-like illness or gastroenteritis.

- **Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected.**
- **If hypersensitivity reaction cannot be ruled out, ZIAGEN or any other medicinal product containing abacavir must not be restarted.**
- The risk is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir hypersensitivity reactions have been reported at a lower frequency in patients who do not carry this allele.
- **ZIAGEN is not recommended for use in patients with the HLA-B*5701 allele or in patients who have had a suspected abacavir HSR while taking any medicinal product containing abacavir.**
- Testing for HLA-B*5701 status is recommended before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- The diagnosis of hypersensitivity reaction is based on clinical judgment. **If a hypersensitivity reaction is suspected, ZIAGEN must be stopped without delay, even in the absence of the HLA-B*5701 allele.** Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in a life-threatening hypotension and death.
- Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity reaction have also experienced life-threatening reactions within hours of re-initiating abacavir therapy. Therefore, if a hypersensitivity reaction is ruled out, the reintroduction of ZIAGEN or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- Each patient should be reminded to read the Consumer Medicine Information. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining ZIAGEN tablets in order to avoid restarting abacavir.

Lactic acidosis/severe hepatomegaly with steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including abacavir, in the treatment of HIV infection. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering ZIAGEN, particularly to those with known risk factors for liver disease. Treatment with ZIAGEN should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Fat loss or fat gain
Fat loss or fat gain has been reported during combination antiretroviral therapy. The long term consequences of these events are currently unknown. A causal relationship has not been established.

Serum lipids and blood glucose
Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune reconstitution syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

General
Opportunistic infections
Patients receiving ZIAGEN or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of HIV associated diseases.

Transmission
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Myocardial infarction
Several observational, epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised controlled trials have observed no excess risk of myocardial infarction with abacavir use. To date there is no established biological mechanism to explain a potential increase in risk. In totality the available data from observational studies and from controlled clinical trials show inconsistency and therefore the evidence for a causal relationship between abacavir treatment and the risk of myocardial infarction is inconclusive.

As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

As part of a triple-drug regimen, ZIAGEN is generally recommended for use with antiretroviral agents from different pharmacological classes and not solely with other nucleoside/nucleotide reverse transcriptase inhibitors. This is based on results from randomised, double-blind, controlled studies in which the proportion of subjects with early virological failure was higher in the triple nucleoside groups than in groups who received regimens involving two nucleosides in combination with an agent from a different pharmacological class. However, consideration needs to be given to a number of factors, including compliance, safety, toxicity and preservation of future treatment options, which also remain important when selecting an appropriate antiretroviral combination for a patient.

Osteonecrosis
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Therapy experienced patients
In clinical trials patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients with prolonged prior NRTI exposure, or who have HIV-1 isolates containing multiple mutations conferring resistance to NRTIs (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Cross resistance).

Special precautions for use
ZIAGEN Oral Solution contains sorbitol which is metabolised to fructose and is therefore unsuitable for patients who have hereditary fructose intolerance.

Sorbitol may cause abdominal pain and diarrhoea.

Use in hepatic impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations.

Use in renal impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations.

Use in the elderly
See Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations.

Paediatric use
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations.

Effects on laboratory tests
See 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Table 3.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The potential for drug interactions involving abacavir is low. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P_{450} 1A1 (CYP1A1). Abacavir shows limited potential to inhibit metabolism mediated by the CYP3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolised by CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolised by major CYP enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

Effect of abacavir on the pharmacokinetics of other agents
In vitro, abacavir demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp) and minimal inhibition of organic cation transporter 1 (OCT1), OCT2 and multidrug and toxin extrusion protein 2-K (MATE2-K). Abacavir is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters. Abacavir is an inhibitor of MATE1 *in vitro,* however abacavir has low potential to affect the plasma concentrations of MATE1 substrates at therapeutic drug exposures (up to 600 mg).

Effect of other agents on the pharmacokinetics of abacavir
In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, Multidrug resistance-associated protein 2 (MRP2) or MRP4, therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations. Although abacavir is a substrate of BCRP and Pgp *in vitro,* clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonovir (Pgp and BCRP inhibitors).

Interactions relevant to abacavir
Ethanol
The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. Given the safety profile of abacavir these findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

Methadone
In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a one hour delay in t_{max}, but the AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone re-titration may be required.

Retinoids
Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Riociguat
In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600 mg/50 mg/300 mg once daily) led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations and for interactions observed in patients receiving highly active antiretroviral therapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Abacavir had no adverse effects on the mating performance of fertility of male and female rats at oral doses of up to 427 mg/kg per day, a dose expected to produce exposures approximately 30 fold higher than that in humans at the therapeutic dose based on AUC.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Use in pregnancy
(Category B3)

The Antiretroviral Pregnancy Registry has received prospective reports of over 2,000 exposures to abacavir during pregnancy resulting in live birth. These consist of over 800 exposures during the first trimester, over 1,100 exposures during the second/third trimester and included 27 and 32 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.0, 4.4%) and in the second/third trimester, 2.7% (1.9, 3.9%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%.

There are no adequate and well-controlled studies in pregnant women. ZIAGEN should be used during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 648 mg/kg during organogenesis (approximately 35 times the human exposure at the recommended dose, based on AUC). In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 427 mg/kg per day. The offspring of female rats treated with abacavir at 427 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 453 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

Use in lactation
There is no data available on the safety of abacavir when administered to babies less than three months old.

Excretion of abacavir in breast milk has been reported in clinical studies, resulting in sub-therapeutic infant plasma levels.

Breast feeding is not advised because of the potential for HIV transmission from mother to child, and the potential risk of adverse events due to antiretroviral drug excretion in breast milk.

In settings where formula feeding is unsafe or unavailable, the World Health Organisation has provided Guidelines.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No currently available data suggest ZIAGEN affects the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial information
The adverse events reported during ZIAGEN therapy in HIV disease were similar in adults and children. For many of these events, it is unclear whether the reported adverse events are related to ZIAGEN, or to the wide range of drugs used in the management of HIV disease or as a result of the disease process.

The following adverse events occurring in more than 10% of patients treated with ZIAGEN

are likely to be drug related: nausea, vomiting, lethargy and fatigue. Other commonly reported adverse events were fever, headache, diarrhoea, and anorexia. In general, adverse events have been transient and not treatment limiting. The majority were mild or moderate in severity. Table 1 lists the most common adverse events, occurring at an incidence of 5% or more, reported in controlled pivotal clinical trials in adults and paediatrics, irrespective of the investigator's assessment of possible relationship to the study drug:

Table 1: Summary of Most Common Adverse Events Reported in ≥ 5% of Subjects CNAAB3003 and CNAA3006

	CNAAB3003† (ABC 300 mg BID dose)		CNAA3006‡‡ (ABC 8 mg/Kg dose)	
Adverse event	**ABC/3TC/ ZDV N=83**	**3TC/ZDV N=81**	**ABC/3TC/ZDV N=102**	**3TC/ZDV N=103**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Number of Subjects reporting any adverse event	76 (92)	70 (86)	88 (86)	89 (86)
Nausea	39 (47)	33 (41)	5 (5)	2 (2)
Headache	26 (31)	16 (20)	16 (16)	12 (12)
Nausea & Vomiting	13 (16)	9 (11)	39 (38)	19 (18)
Malaise & fatigue	28 (34)	20 (25)	5 (5)	1 (1)
Diarrhoea	10 (12)	9 (11)	16 (16)	15 (15)
Cough	6 (7)	5 (6)	24 (24)	12 (12)
Ear, nose & throat infection	3 (4)	8 (10)	19 (19)	17 (17)
Temperature regulation disturbance	4 (5)	6 (7)	19 (19)	12 (12)
Feeding problems	9 (11)	8 (10)	9 (9)	2 (2)
Skin rashes	4 (5)	4 (5)	11 (11)	8 (8)
Nasal signs & symptoms	4 (5)	7 (9)	11 (11)	8 (8)
Sleep disorders	6 (7)	4 (5)	1 (1)	0
Viral ear, nose & throat infection	6 (7)	5 (6)	9 (9)	5 (5)
Abdominal discomfort & pain	3 (4)	6 (7)	5 (5)	7 (7)
Decreased white cells	4 (5)	3 (4)	4 (4)	5 (5)
Neuropathy	1 (1)	3 (4)	2 (2)	1 (1)
Musculoskeletal pain	6 (7)	4 (5)	3 (3)	4 (4)

ABC = Abacavir; 3TC = lamivudine; ZDV = zidovudine

† Dose of 3TC 150 mg bd and ZDV 300 mg bd

‡‡ Dose of 3TC 4 mg/kg bd and ZDV 180 mg/m^2 bd

Table 2 lists the most common grade 2 to 4 adverse events, occurring at an incidence of 5% or more:

Table 2: Most Common (Greater than or equal to 5% Incidence) Grade 2 to 4 Adverse Events (Safety Population - CNA30021)

Adverse Event	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY Grade 2 to 4 AE	267 (70%)	276 (72%)
Drug hypersensitivity	35 (9%)	27 (7%)
Insomnia	26 (7%)	36 (9%)
Depression	25 (7%)	26 (7%)
Diarrhea	21 (5%)	25 (6%)
Nausea	21 (5%)	25 (6%)
Headache	21 (5%)	21 (5%)
Rash	21 (5%)	19 (5%)
Fatigue	20 (5%)	29 (8%)
Dizziness	19 (5%)	19 (5%)
Pyrexia	19 (5%)	13 (3%)
Abnormal dreams	15 (4%)	19 (5%)
Anxiety	12 (3%)	20 (5%)

In controlled clinical studies laboratory abnormalities related to ZIAGEN treatment were uncommon, with no differences in incidence observed between ZIAGEN treated patients and the control arms. Refer to Table 3.

Table 3: Grade 3 to 4 Treatment Emergent Laboratory Abnormalities (Safety Population - CNA30021)

Grade 3 and 4 Laboratory Abnormalities	ABC OAD N=384 N (%)			ABC BID N=386 N (%)		
Clinical Chemistry	**Gr 3**	**Gr 4**	**Gr 3-4**	**Gr 3**	**Gr 4**	**Gr 3-4**
Elevated ALT	14 (4%)	9 (2%)	23 (6%)	18 (5%)	6 (2%)	24 (6%)
Elevated AST	10 (3%)	13 (3%)	23 (6%)	9 (2%)	5 (1%)	14 (4%)
Alkaline phosphatase	1 (< 1%)	0	1 (< 1%)	0	1 (< 1%)	1 (< 1%)
Amylase	13 (3%)	2 (< 1%)	15 (4%)	12 (3%)	0	12 (3%)
Bilirubin	0	2 (< 1%)	2 (< 1%)	1 (< 1%)	1 (< 1%)	2 (< 1%)
Creatine kinase	13 (3%)	31 (8%)	44 (12%)	13 (3%)	22 (6%)	35 (9%)
Creatinine	0	0	0	0	1 (< 1%)	1 (< 1%)
Glucose	4 (1%)	1 (< 1%)	5 (1%)	5 (1%)	0	5 (1%)
Sodium	2 (< 1%)	0	2 (< 1%)	1 (< 1%)	0	1 (< 1%)
Triglycerides	13 (3%)	5 (1%)	18 (5%)	13 (3%)	8 (2%)	21 (6%)
Hematology						
Hemoglobin	0	1 (< 1%)	1 (< 1%)	0	0	0
Neutrophils absolute	6 (2%)	3 (< 1%)	9 (2%)	4 (1%)	1 (< 1%)	5 (1%)
Platelets	2 (< 1%)	0	2 (< 1%)	2 (< 1%)	0	2 (< 1%)
WBC	0	0	0	1 (< 1%)	0	1 (< 1%)

Other information

Many of the adverse events listed below (nausea, vomiting, diarrhoea, fever, fatigue, rash) occur commonly as part of abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If

ZIAGEN has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart ZIAGEN, this should be done only under direct medical supervision (see Special considerations following an interruption of ZIAGEN therapy).

The following adverse events may be related to ZIAGEN. The majority of these have not been treatment limiting.

Metabolism and nutrition disorders
Common: anorexia, hyperlactataemia
Rare: lactic acidosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Nervous system disorders
Common: headache

Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea
Rare: pancreatitis has been reported, but a causal relationship to ZIAGEN treatment is uncertain.

Skin and subcutaneous tissue disorders
Common: rash (without systemic symptoms)
Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

General disorders and administration site disorders
Common: fever, lethargy, fatigue.

In controlled clinical studies, laboratory abnormalities related to ZIAGEN treatment were uncommon, with no differences in incidence observed between ZIAGEN treated patients and the control arms.

Description of selected adverse effects
Hypersensitivity to abacavir (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in **at least 10% of patients** with a hypersensitivity reaction are in bold text.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin:	**rash** (usually maculopapular or urticarial)
Gastrointestinal tract:	**nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration

Respiratory tract:	**dyspnoea**, **cough,** sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous:	**fever, fatigue, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry:	**headache**, paraesthesia
Haematological:	lymphopenia
Liver/pancreas:	**elevated liver function tests,** hepatic failure
Musculoskeletal:	**myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology:	elevated creatinine, renal failure

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

For details of clinical management in the event of a suspected abacavir HSR see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Paediatric population

The safety database to support abacavir once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials). Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing (see Table 4). One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

Table 4: ARROW Study Randomization 3: Most Frequently Reported (2 or More Events Overall) of Grade 3 or 4 Adverse Events for Once- Versus Twice-Daily Dosing of Abacavir and Lamivudine by Dosing Frequency and Overall

	Twice-Daily ABC+3TC	**Once-Daily ABC+3TC**	**Total**
Total number of subjects	333	336	669
Total grade 3 or 4 AEs, n (%)	82 (25)	95 (28)	177 (26)
Hematological: computer, n (%)			
Leucopenia	2 (< 1)	1 (< 1)	3 (< 1)
Neutropenia	15 (5)	23 (7)	38 (6)
Non-clinical anaemia	6 (2)	3 (< 1)	9 (1)
Thrombocytopenia	6 (2)	10 (3)	16 (2)
Biochemical: computer, n (%)			
Hypoglycaemia	0	2 (< 1)	2 (< 1)
Raised ALT	5 (2)	1 (< 1)	6 (< 1)
Raised AST	3 (< 1)	4 (1)	7 (1)

	Twice-Daily ABC+3TC	Once-Daily ABC+3TC	Total
Raised bilirubin	2 (< 1)	1 (< 1)	3 (< 1)
Raised liver enzymes	3 (< 1)	5 (1)	8 (1)
Hematological: clinical report, n (%)			
Anaemia with clinical symptoms	5 (2)	7 (2)	12 (2)
Thrombocytopenia	0	2 (< 1)	2 (< 1)
Specific Infections, n (%)			
Measles	3 (< 1)	1 (< 1)	4 (< 1)
Plasmodium falciparum malaria	16 (5)	16 (5)	32 (5)
Presumptive septicemia/bacteremia	3 (< 1)	3 (< 1)	6 (< 1)
Diarrheal disease, n (%)			
Acute diarrhea, not investigated	2 (< 1)	2 (< 1)	4 (< 1)
Lower respiratory tract, n (%)			
Pneumonia, no organism identified	2 (< 1)	2 (< 1)	4 (< 1)
Eye, n (%)			
Cataract	0	2 (< 1)	2 (<1)
Undiagnosed fevers, n (%)			
Acute febrile episode	0	2 (< 1)	2 (<1)
Unknown, n (%)			
Dog bite	0	2 (< 1)	2 (<1)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. If overdosage occurs the patient should be monitored for evidence of toxicity (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Abacavir is a nucleoside analogue reverse transcriptase inhibitor. It is a selective antiretroviral agent against HIV-1 and HIV-2, including HIV-1 isolates with reduced susceptibility to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'-triphosphate (TP). *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV

reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. The antiviral activity of abacavir against HIV-1 strain IIIb in cell culture *in vitro* was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

In a study of 20 HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the sampling time, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours. The steady state pharmacokinetic properties of abacavir 600 mg once daily was compared to abacavir 300 mg twice daily in a crossover study in 27 HIV-infected patients. Intracellular carbovir triphosphate exposures in peripheral blood mononuclear cells were higher for abacavir 600 mg once daily with respect to $AUC_{24,ss}$ (32% higher), $C_{max\ 24,ss}$ (99% higher) and trough values (18% higher), compared to the 300 mg twice daily regimen. These data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients. Additionally, the efficacy and safety of this combination given once daily has been demonstrated in a pivotal clinical study (CNA30021- see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that reverse transcriptase amino acid residue 184 was consistently the most frequent position for NRTI resistance-associated mutations (M184V or M184I). The second most frequent mutation was L74V. Mutations Y115F and K65R were uncommon. In a study of therapy-naive adults receiving ZIAGEN 600 mg once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (Study CNA30021), there was a low overall incidence of virologic failure at 48 weeks in both the once and twice daily treatment groups (10% and 8% respectively). Additionally for technical reasons genotyping was restricted to samples with plasma HIV-1 RNA > 500 copies/mL. This resulted in a small sample size. Therefore no firm conclusions could be drawn regarding differences in treatment emergent mutations between the two treatment groups. Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the abacavir- and lamivudine-associated resistance mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%, 8/20). L74V, Y115F and K65R were the other RT mutations observed in the study.

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a > 2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13). Fifty-six percent (10/18) of the virologic failure isolates in the once-daily abacavir group compared to 41% (7/17) of the failure isolates in the twice-daily abacavir group had a > 2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range 0.79 to > 116) and 1.1 (range 0.68 to > 116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-resistance
Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors.

Viruses containing abacavir and lamivudine resistance-associated mutations, namely, M184V, L74V, Y115F and K65R, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine *in vitro* and in patients. The M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine and the K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the L74V plus the M184V/I mutation, viruses with K65R with or without the M184V/I mutation, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

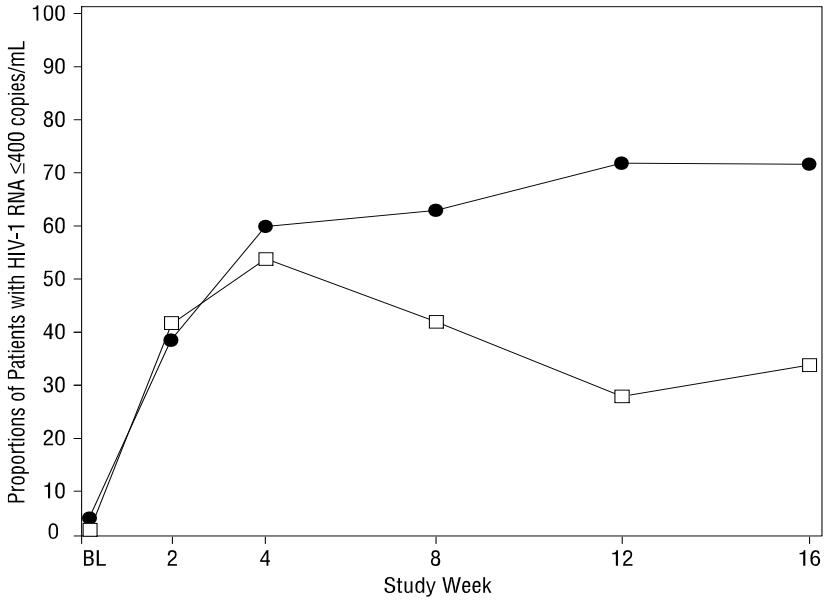
Clinical trials

Description of clinical studies

Therapy-naive adults

CNAAB3003 is an ongoing, multicenter, double-blind, placebo-controlled study in which 173 HIV-infected, therapy-naive adults were randomised to receive either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and zidovudine (300 mg twice daily) or lamivudine (150 mg twice daily) and zidovudine (300 mg twice daily). The duration of double-blind treatment was 16 weeks. Study participants were: male (76%), Caucasian (54%), African-American (28%), and Hispanic (16%). The median age was 34 years, the median pretreatment CD4 cell count was 450 cells/mm^3, and median plasma HIV-1 RNA was 4.5 log_{10} copies/mL. Proportions of patients with plasma HIV-1 RNA ≤ 400 copies/mL (using Roche Amplicor HIV-1 MONITOR® Test) through 16 weeks of treatment are summarised in Figure 1.

Figure 1: Proportions of Patients with HIV-1 RNA ≤400 copies/mL in Study CNAAB3003[1]



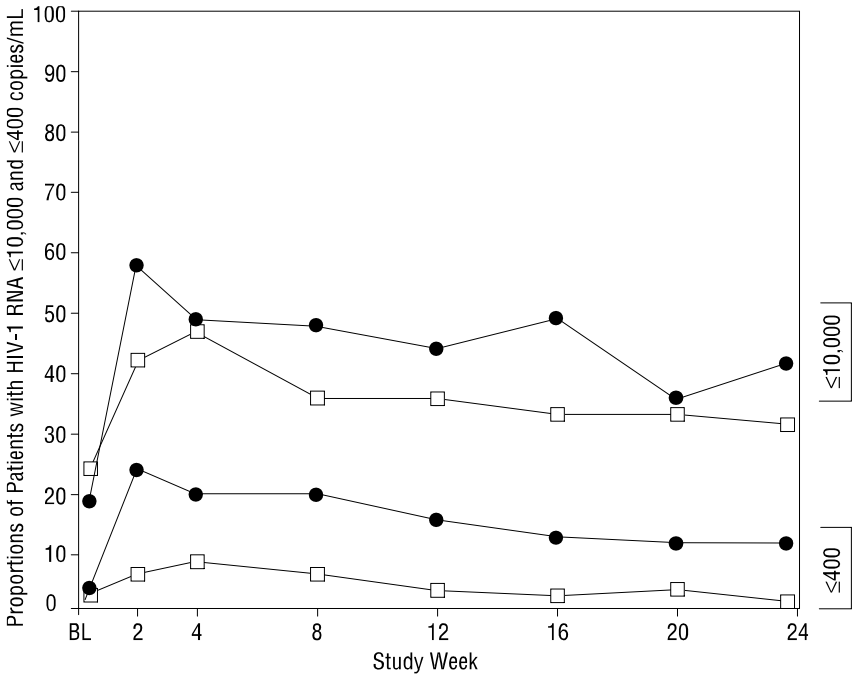
[1]Missing data were considered as HIV-1 RNA >400 copies/mL.

After 24 weeks of therapy, the median CD4 increases from baseline were 87 cells/mm^3 in the group receiving ZIAGEN and 86 cells/mm^3 in the placebo group.

Therapy-experienced paediatric patients

CNAA3006 is an ongoing, randomised, double-blind study comparing ZIAGEN 8 mg/kg twice daily and lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily. Two hundred and five paediatric patients were enrolled: female (56%), Caucasian (17%), African-American (50%), Hispanic (30%), median age of 5.4 years, baseline CD4 cell percent > 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 $\log_{10}$ copies/mL. Eighty percent and 55% of patients had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. Proportions of patients with plasma HIV-1 RNA levels ≤ 10,000 and ≤ 400 copies/mL, respectively, through 24 weeks of treatment are summarised in Figure 2.

Figure 2: Proportions of Patients with Plasma HIV-1 RNA ≤10,000 copies/mL or ≤400 copies/mL Through Week 24 in Study CNAA3006[1,2]



[1]Missing data were considered as above the HIV-1 RNA threshold.
[2]No significant difference was observed at 24 weeks for the ≤10,000 copies/mL threshold.

After 24 weeks of therapy, the median CD4 change from baseline was an increase of 47 cells/mm^3 in the group receiving ZIAGEN and a decrease of 10 cells/mm^3 in the control group.

Abacavir penetrates the cerebrospinal fluid (CSF) (see Section 5.2 PHARMACOKINETIC PROPERTIES), and has been shown to reduce HIV-1 RNA levels in the CSF. However, in a double-blind randomised clinical study of abacavir sulfate 600 mg twice a day added to

background therapy in AIDS dementia, no significant difference compared with placebo was shown for neuropsychological performance (the primary endpoint).

Once daily

A once daily regimen of abacavir was investigated in a multicentre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. They were randomised to receive either abacavir 600 mg once daily or 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. Patients were stratified at baseline based on plasma HIV-1 RNA ≤ 100,000 copies/mL or > 100,000 copies/mL. The duration of double-blind treatment was at least 48 weeks. The results are summarised in the table below:

Table 5: Virological Response Based on Plasma HIV-1 RNA <50 copies/ml at Week 48 ITT-Exposed Population

Populations	ABC once/day + 3TC + EFV (N = 384)	ABC twice/day + 3TC + EFV (N = 386)	Point Estimate	95% CI*
Stratified			-1.7	-8.4, 4.9
Sub-group by baseline RNA				
≤ 100,000 copies/mL	141/217 (65%)	145/217 (67%)	-1.8	-10.8, 7.1
> 100,000 copies/mL	112/167 (67%)	116/169 (69%)	-1.6	-11.6, 8.4
Total population	253/384 (66%)	261/386 (68%)		

* Confidence interval

The abacavir once daily group was demonstrated to be non-inferior when compared to the twice daily group in the overall and base-line viral load sub-groups. The incidence of adverse events reported was similar in the two treatment groups.

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients, conducted in Uganda and Zimbabwe. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). Subjects were ART naïve before enrolment and initiated treatment with an NNRTI + ABC (twice daily) + 3TC (twice daily) with or without ZDV. After 36 weeks on antiretroviral therapy which included twice daily abacavir and lamivudine, 669 eligible children who had been on ART for at least 36 weeks, were currently taking lamivudine + abacavir twice daily as part of their ART regimen and expected to stay on these two drugs for at least the next 12 weeks were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. At the time of the once daily versus twice daily randomization, median age was 5.5 years (range 1.8 - 16.9 years). Most subjects (58.9%) were WHO Stage 3 and most subjects (68.5%) had CD4 at ≥ 30%. The results are summarised in the table below:

Table 6: Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	**Once Daily N (%)**
Week 0 (After ≥ 36 Weeks on Treatment)		
Plasma HIV-1 RNA < 80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA < 80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA < 80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir/lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of < 80 copies/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (< 200 copies/mL, < 400 copies/mL, < 1000 copies/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

Note that the endpoint of viral load < 50 copies/mL could not be assessed due to low volumes of stored plasma samples from small children.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Abacavir is rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%. Following oral administration, the mean time to maximal serum concentrations (t_{max}) of abacavir is about 1.5 hours for the tablet formulation and about 1.0 hour for the solution formulation.

There are no differences observed between the AUC for the tablet or solution. At a dosage of 300 mg twice daily, the mean steady state C_{max} of abacavir from tablet administration was 3.00 µg/mL, and the mean AUC over a dosing interval of 12 hours was 6.02 µg.h/mL (daily AUC of approximately 12.0 µg.h/mL). The C_{max} value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean abacavir C_{max} was approximately 4.26 µg/mL and the mean AUC was 11.95 µg.h/mL.

Food delayed absorption of abacavir and decreased the C_{max} but did not affect overall plasma concentrations (AUC). The clinical significance is not known.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic characteristics of the active ingredients and the *in vitro* dissolution behaviour of abacavir tablets in water, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution
Following intravenous administration, the apparent volume of distribution was about 0.8 L/kg, indicating that abacavir penetrates freely into body tissues.

Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. In a Phase I pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1.5 hours post dose was 0.14 µg/mL. In a further pharmacokinetic study using 600 mg abacavir twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13 µg/mL at 0.5 to 1 hour after dosing, to approximately 0.74 µg/mL after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9 fold greater than the IC_{50} of abacavir of 0.08 µg/mL or 0.26 µM.

In vitro studies indicate that at therapeutic concentration plasma protein binding capacity of abacavir is low to moderate (~49%). This indicates a low likelihood for drug interactions through plasma protein binding displacement.

Metabolism
Abacavir is primarily metabolised by the liver with less than 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine.

Excretion
The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant drug accumulation. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine; the remainder is eliminated in the faeces.

Special populations

Hepatically impaired
Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). The results showed that there was a mean increase of 1.89 fold in the abacavir AUC, and 1.58 fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease.

However, the rates of formation and elimination of these were decreased.

In order to achieve exposures that are within the therapeutic range of patients without liver disease, patients with mild hepatic impairment should receive 200 mg abacavir twice daily. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, therefore ZIAGEN is not recommended in these patients. (See also Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Renal impairment

The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Children

Abacavir is rapidly and well absorbed from oral solution and tablet formulations administered to children. Plasma abacavir exposure has been shown to be the same for both formulations when administered at the same dose. Children receiving abacavir oral solution according to the recommended dosage regimen achieve plasma abacavir exposure similar to adults. Children receiving abacavir oral tablets according to the recommended dosage regimen achieve higher plasma abacavir exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Paediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose for both oral solution and tablet formulations. However, C_{max} is approximately 2-fold higher with once daily dosing compared to twice daily dosing.

Table 7: Pharmacokinetic Parameters [Geometric Mean (95% CI)] after Repeat Dosing of Abacavir in 3 Paediatric Trials

	Trial (Number of Subjects)					
	ARROW PK (n = 36)		**PENTA-13 (n = 14)**		**PENTA-15 (n = 18)[a]**	
Age Range	3-12 years		2-12 years		3-36 months	
Formulation	Tablet		Solution and Tablet[b]		Solution	
Parameter	Once Daily	Twice Daily	Once Daily	Twice Daily	Once Daily	Twice Daily
C_{max} (mcg/mL)	6.84 (5.92-7.90)	4.18 (3.69-4.73)	4.80 (4.04-5.71)	2.14 (1.79-2.56)	4.68 (3.86-5.67)	2.29 (1.80-2.91)
$AUC_{(0-24)}$ (mcg•h/mL)	15.3 (13.3-17.5)	15.6 (13.7-17.8)	13.4 (11.8-15.2)	9.91 (8.26-11.9)	11.6 (9.89-13.5)	10.9 (8.89-13.2)

[a] N = 17 for PENTA-15 C_{max}.

[b] 2 subjects in PENTA-13 received abacavir tablets.

Elderly

The pharmacokinetics of abacavir have not been studied in patients over 65 years of age. When treating elderly patients consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, and concomitant disease or other drug therapy.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Abacavir was inactive in *in vitro* tests for gene mutation in bacteria but it showed clastogenic activity against human lymphocytes *in vitro* and in an *in vivo* mouse micronucleus test. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was not mutagenic in bacterial mutagenicity assays.

Carcinogenicity
Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver, urinary bladder, lymph nodes and the subcutis of female rats.

Nonmalignant tumours occurred in the liver of mice and rats, Harderian gland of female mice, and thyroid gland of rats. In rats, there were also increased incidences of urothelial hyperplasia and urinary bladder tumours, associated with increased urinary calculi.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. These dose levels were equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg. This is equivalent to six times the expected human systemic exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ZIAGEN tablets

Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Colloidal anhydrous silica
Glycerol triacetate
Hypromellose
Titanium dioxide
Polysorbate 80
Iron oxide yellow

ZIAGEN oral solution

Sorbitol solution (70%),
Saccharin sodium
Sodium citrate dihydrate
Citric acid
Methyl hydroxybenzoate
Propyl hydroxybenzoate

Propylene glycol
Artificial strawberry
Artificial banana flavour
Purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tablets
Store below 30°C.

Oral solution
Store below 30°C.

The oral solution should be discarded two months after first opening.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets
ZIAGEN tablets are supplied in polyvinyl chloride/foil blister packs or polyvinyl chloride/child resistant* foil blister packs containing 60 tablets.
*complies with European Standard *EN 14375:2003 Child-resistant Non-reclosable Packaging for Pharmaceutical Products - Requirements And Testing.*

Oral solution
ZIAGEN Oral Solution is supplied in high density polyethylene (HDPE) bottles containing 240 mL of oral solution.

A 10 mL oral dosing syringe and an adapter are also included in the pack for accurate measurement of the prescribed dose.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

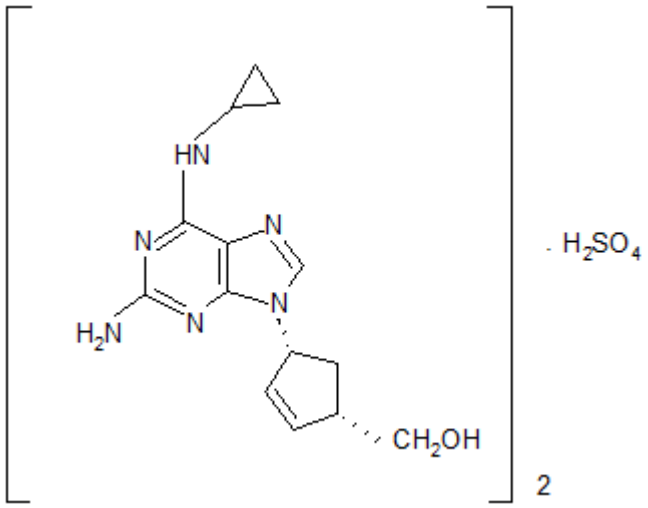
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name of abacavir sulfate is [4*R*-(2-Amino-6-cyclopropylamino-purin-9-yl)-cyclopent-2-en-1*S*-yl]-methanol sulfate (2:1).

The molecular formula of abacavir sulfate is $(C_{14}H_{18}N_6O)_2.H_2SO_4$ and it has a relative molecular mass of 670.76.

Chemical structure
Abacavir sulfate has the following structural formula:



CAS number
188062-50-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067
Australia

9 DATE OF FIRST APPROVAL

9 June 1999

10 DATE OF REVISION

28 September 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Update to transmission of infection
4.5	Addition of a potential drug-drug interaction between abacavir and riociguat

Version 16.0